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13. ABSTRACT (Maximum 200 Words)
Microwave hyperthermia has shown promise in the treatment of malignant breast tumors with minimal side effects due to the use of non-ionizing radiation. However the full potential has yet to be realized due to technological limitations. This project aimed to improve this technology in two areas. The first area of research is developing biocompatible vectors with high microwave absorbing and scattering materials. These would enhance in-vivo localization of target cells, where the activity of specific markers is present. The second area of research seeks to optimize the microwave energy delivery system, studying the efficiency of pulsed/continuous energy deposition for frequency from 30 MHz to 3 GHz, where the hyperthermia has shown best therapeutic results therapy and detection systems are designed. In these two years of research only part of the first issue was addressed, identifying and measuring biocompatible materials that would enhance the absorption and/or the scattering of microwave photons in water based inhomogeneous medium. The first year was dedicated to deepening our understanding of dipolar polarization and conduction mechanisms, which determine the efficiency of microwave heating. A measurement system was then established and a series of measurements was taken on water-soluble conductive polymers. The first measurements on conductive polymers showed promising results, while the water isotopes didn't show the desired absorbing behavior in the liquid state. Future research work could be aimed to better understand their absorption mechanism as well as to include these materials in liposomes and optimize the external delivery system.

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Introduction

Microwave hyperthermia has shown promise in the treatment of malignant breast tumors with minimal side effects due to the use of non-ionizing radiation. However the full potential has yet to be realized due to technological limitations. This project seeks to move this technology toward its full potential in two areas.

The first area of research was dedicated to deepening our understanding of how hyperthermia works and what systems are now available. Following this study, we suggest an optimized microwave energy delivery system, for efficient energy deposition for frequency from 30 MHz to 3 GHz, where the hyperthermia has shown best therapeutic results therapy and detection systems are designed. The system could be realized with further future research and funding efforts.

The second area of research is developing biocompatible vectors with high microwave absorbing and scattering materials. These would enhance in-vivo localization of target cells, where the activity of specific markers such as Telomerase or Hepatocyte Growth Factor is present.

Due to a delay in the delivery of the measurement system for microwave material characterization and a 6-month leave of absence of the PI, a one-year no-cost extension was approved. The following technical report is based on the results obtained in the period May 2001 – July 2003.

Part 1: Theoretical study of a new hyperthermia system using a confocal scanning technique.

Background

In recent years, much attention has been addressed to radio-frequency (RF) and microwave (MW) electromagnetic emission for new generations of communication systems. The 0.3-30 GHz radiation spectrum (photon energy from 1.23 to 123 μeV) is now being exploited for several applications. Until very recently, the cost and availability of the instrumentation has limited the use of this spectrum to military or niche commercial environments, but the explosion of wireless technologies has led to dramatic reductions in costs, and the creation of extensive national infrastructure for RF and MW electronics. In particular, MMIC (Microwave Monolithic Integrated Circuit) technology is now commonplace in this spectral range, and currently used extensively in cell phones, wireless Internet, automotive radar, and satellite systems. Using these new technologies, arrays of RF and MW antennas can be designed to easily direct and focus energy exactly where it is needed. Such "spot-beam" technology is emerging in satellite and terrestrial communications, and is a focal point of research activity at UCSB.

However, medical applications using photons at such energies are very rare, mainly for two reasons. First, studies of the effects of microwave radiation on biological tissues are very limited, and so the interactions between low-energy photons and bio-entities (enzymes, proteins, whole cells, etc.) are not well understood. Second, the inhomogeneity of the human body complicates the trajectory of the photons at MW frequencies and makes their control and the interpretation of the results a difficult task.

On the other hand, while X-rays, ultraviolet, visible and infrared photons have enough energy to induce chemical reactions such as dissociation and thus may cause irreversible tissue damage also at low power exposure (few photons per unit area per unit time), MW photons seem to merely induce thermal vibrations with a consequent increase of temperature. Small thermal changes are well supported by human tissues, and it is only at high power (thus high concentration of photons per unit area) that the resulting increase of temperature is enough to cause cell death: low doses of RF or MW radiation do not affect the cell activity, because the photon energy at these frequencies is too low.

Moreover, while MW and X-rays can penetrate the human body, most of the other photon radiation is not able to reach deep tissues because of skin reflection and tissues absorption. Thus, high-energy photon radiators (such as lasers) can find useful application only for surface treatment. Furthermore, the advantages offered by the X-rays—deep tissue interaction and high-resolution imaging—are offset by the disadvantages of cell ionization and extreme difficulty in controlling and focusing the beam distribution. *Thus, the possibility to create and scan a coherent spot of high photon concentration inside deep tissues, with low side effect risk, is a unique property of MW radiation.*

Three recent discoveries in conjunction with an established therapy technique have led us directly to a novel idea for accurate detection and potential destruction of malignant cells using microwave radiation. The key concepts are:

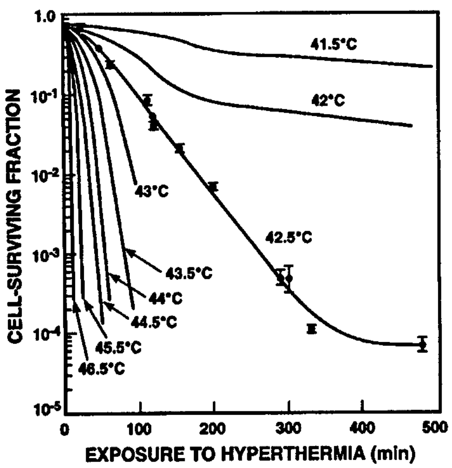
- Microwave hyperthermia, a currently used and promising therapy for thermal destruction of cancerous forms.
- Microwave adaptive phased-array antennas, which only lately can be implemented efficiently in the frequency range of interest due to the impressive technological progresses in the microwave communication market
- Implementation of a confocal scanning technique for small breast tumor detection microwave system
- Recent discovery of human Telomerase with the continuous progresses in understanding its role in cancer.

In the following we examine these areas briefly, followed by a description of the proposed innovative hardware.

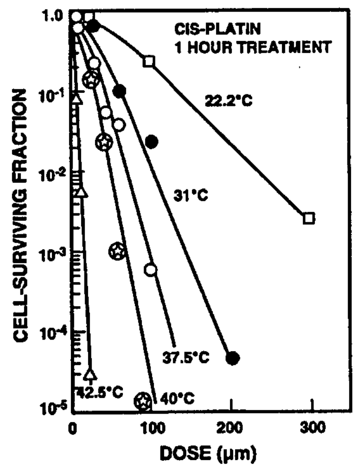
Microwave Hyperthermia

Hyperthermia is a procedure in which body tissue is exposed to a raise in temperature in order to induce therapeutic effect. Although not widely known, hyperthermia has shown promising results in its trial phase in the treatment of cancer. Evidences show that hyperthermia therapy can shrink tumors by damaging cells or depriving them of substances they need to live on [1]. Currently trials are ongoing for local, regional, and whole-body hyperthermia, using external and internal heating devices. Hyperthermia is generally used with other methods of therapy (radiation therapy, chemotherapy, and biological therapy) in an attempt to increase their effectiveness [2](see figure 1).

The efficacy of microwave hyperthermia relies on the fact that most tumor cells have significantly (up to 20%) more water than normal cells, and water is highly absorbing in the microwave region. Thus upon microwave irradiation, tumor cell will heat up more rapidly than the healthy surrounding tissue. The photons are absorbed, but they do not cause dissociation/ionization: they can only excite vibrational and rotational modes of polar molecules as described in [3].



Survival curves for mammalian cells in culture (Chinese hamster CHO line) heated at different temperatures for varying lengths of time. (Redrawn from Dewey WC, Hopwood LE, Sapareto SA, Gerwech LE: Radiology 123:463–474, 1977)



Effect of elevated temperatures on the cytotoxicity of cisplatin in V79 hamster cells in vitro. Cells were heated for 1 hour at the temperatures indicated. (From Roizin-Towle L, Hall EJ, Capuano L: NCI Monogr 61:149–151, 1982)

Figure 1 – Cellular response to heat (see text above for references).

Ultrasound and microwave hypothermia treatments are quite effective on their own and combined with radiation/chemo-therapies they lead to remarkable results (67% of partial and total responses reported at the Valley Cancer Institute in LA - Ca) [4]. Conventional hyperthermia instruments (fig. 2) use microwave energy (915 MHz) to heat the treated area, and keep the temperature at about 42.5°C (108.5°F).

Figure 2 - Conventional machines used at the Valley Cancer Institute in LA – Ca. Microwave unfocused energy at 915 MHz is used to heat the treated area, and keep the temperature at about 42.5°C (see also previous cellular response).

The photographs and MRI pictures of figure 3 were taken before and after hyperthermia combined with low X-radiation dose. Hyperthermia does not cause any marked increase in radiation side effects or complications. Heat applied directly to the skin, however, can cause discomfort or even significant local pain in about half the patients treated. As shown in fig. 3, it can also cause blisters, which generally heal rapidly. Less commonly, it can cause burns.

Figure 3 - Adenocarcinoma and brain tumor: before and after treatment [4]

Another concern of this treatment is the small selectivity of the photon beam using conventional microwave sources: the "spot" size is usually much larger than the tumor itself and this may increase the temperature of the surrounding healthy tissue. Furthermore the tumor is illuminated from one or two directions only, and usually incoherently, so the spatial energy distribution cannot be shaped. Finally, there is a need to probe the local temperature. This has been achieved with invasive techniques (like small sensors), but typically the slow response time and the use of a solitary probe seriously reduces the ability to resolve the temperature distribution.

Skin burn, large spot size (when applied at 1 GHz), and the use of a single unfocused high-energy beam are the limitations of this therapy that we intend to eliminate.

Why hyperthermia works?

Previously reported clinical results show some of the reason why hyperthermia works:

- When cancer cells multiply, they eventually require more blood/oxygen than their existing blood vessels can supply. In response to this, the tumors stimulate the growth of new blood vessels, but these vessels are mutated, formed in odd sizes, or even with loops or blind ends.
- In these mutated vessels, blood flows slowly and irregularly. Because of this, the tumor is not receiving as much oxygen as it needs, and also, because blood circulation is the body's main "cooling system," the tumor is liable to overheat.
- When the tumor is heated up through hyperthermia, it is unable to sufficiently cool down, and so it is vulnerable to destruction at these elevated temperatures.
- The plasma membranes, cytoskeleton and cell nucleus in these cancerous cells are believed by scientists to all be damaged beyond repair by hyperthermia.
- Hyperthermia has been used in combination with chemotherapy because heating increases membrane permeability (in cells that are not destroyed completely) and the potency of some drugs.

It has been proven to:

- Increase local tumor control and disease-free survival time
- Decrease the relative incidence of disease associated with cancer, as well as the incidence of disease associated with other cancer treatments, which decreases the patient care costs.
- Provide the patient improved quality of life.
- Provide an effective treatment for previously non-treatable tumors.
- Increase the efficacy of radiation and chemotherapy to a significant degree without an increase in toxicity.
- Increase the range of tumors that may be effectively treated using chemotherapy (by providing a supra-additive effect on several chemotherapeutic agents).
- Be used as presurgical treatment to reduce the tumor size prior to resection, allowing patients with large tumors to have their tumors resected without amputation or removal of normal tissue structures.
- Allow clinician to reduce the chemotherapy and/or radiation dose without sacrificing efficacy, thus reducing the debilitating and dangerous side effects of these treatments.
- Hyperthermia is one of the few new cancer treatments that have been clinically proven and one of the only cancer treatments that offers increased disease-free survival and reduced toxicity.

High Power, Highly Focused Adaptive Phased Array

Arrays of antennas can resolve some of the problems described above. Using a number of small antennas distributed over a large area, a tightly focused beam can be generated whereby the individual antennas radiate modest energy but the collective energy in the beam can be significant [5,6]. By electronically controlling the coherent amplitude and phase distribution in the antenna array, the beam direction or focal point can be accurately scanned through space. Until recently, the practical use of phased arrays has been limited to military use by the extremely high cost of the systems. However, cost-effective arrays can now be constructed using commercially available components at microwave frequencies.

Recently phased arrays have been used to dramatically increase the effectiveness of microwave hyperthermia therapy (in mouse trials) while keeping the skin temperature low [7,8]. Multiple sources located in different positions, radiate pulsed power that will combine constructively only in a small spot. The photon concentration in this spot can be very high and the temperature is expected to increase drastically compared to the surrounding tissues. As shown in fig. 1, in 8 min at 45 °C living cells die. The more precisely focused the beam, the more limited is the damage to the nearby cells. Fenn [7,8] performed such an experiment using a rudimentary phased-array with only two sources. *The use of multiple arrays, each with lower power but maintaining the same collective power, can increase drastically the total energy in the focus point, while reducing the skin temperature.*

The electrical inhomogeneity of body tissue complicates the process of illuminating a tumor. Therefore, in order to be successful, this technique requires a feedback system to adaptively correct the beam location and spot shape. A metal needle inside the tumor can provide rapid feedback by collecting (as an antenna) some of the incoming power. This method is simple but is invasive, uncomfortable, and unable to provide complete information on the actual spatial distribution of microwave energy in the body. *Our approach will make use of a new technique of confocal imaging in conjunction with surface thermal sensing to locate the position of a tumor.*

Microwave Confocal Scanning

Confocal scanning is a new, fast, non-invasive, and accurate (~1 mm resolution) detection system that has been proposed for breast tumor detection[9]. The technique was initially developed in the context of ground-penetrating radar to detect the presence of deep land-mines [10]. It works best when dielectric properties of the surrounding medium and the target (tumor) are significantly different [11], which is generally true in cases of interest for this proposal (fig. 4). For example, breast tissue is mostly fat with a low dielectric constant, while the tumor has a higher concentration of water and hence larger dielectric constant and stronger RF and MW absorption.

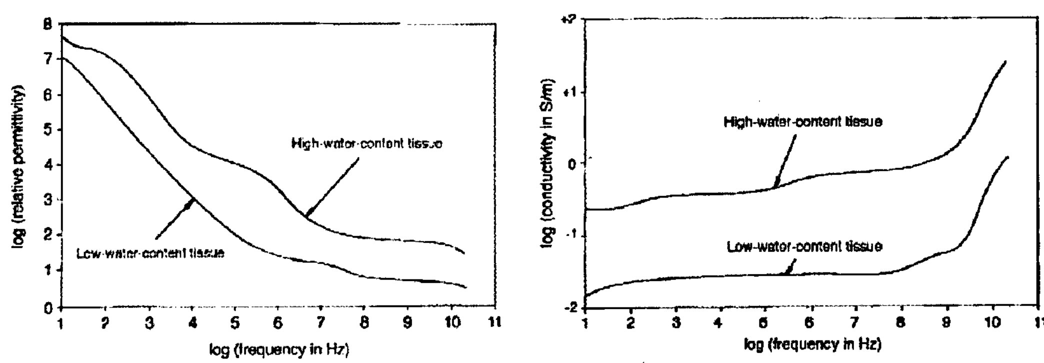


Figure 4 - Comparison of permittivity and conductivity of high-water-content tissue such as muscle with low-water-content tissue such as fat as a function of frequency according to Gabriel [15].

In the confocal imaging technique, an array of antennas is positioned around the subject. Each antenna is sequentially excited by a short pulse and records the time-dependent backscattered signal from the subject, exactly like an aircraft radar system. Using some knowledge of the average propagation velocity for waves in the medium, the recorded signals from each antenna can then be summed with appropriate time delays to compute a scattering cross-section from a "virtual" focal point. This focal point can be effectively scanned throughout the subject by varying the numerical time-delays. The presence of a significant inhomogeneity (tumor) would then show up as a sharp peak in the intensity of the combined received signal when the virtual focus is located at the tumor site. Figure 5 illustrates the results of some electromagnetic simulations for this method, using published data for the dielectric properties of breast tissue. It has been showed that this technique is adequate to detect small cancerous tumors usually missed by X-rays mammography.

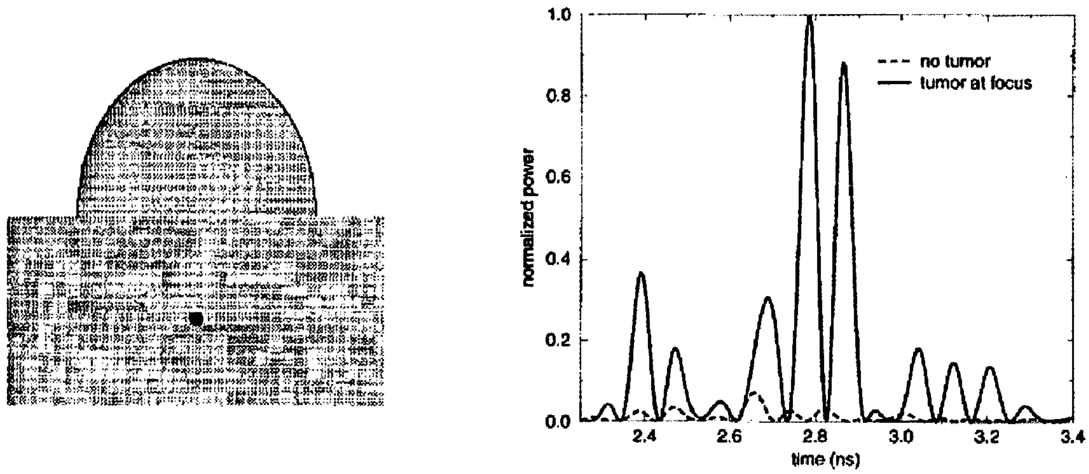


Figure 5 – (from reference [9]). 2-D FDTD computational model of the elliptical reflector system studied by Taflove, showing the heterogeneous breast tissue model and a 5 mm-diameter tumor located at the in-breast focus 3.8 cm beneath the surface, (b) FDTD-computed time-domain waveforms of the backscattered response with and without the tumor present at the in-breast focus.

Proposed Detection & Therapy

The proposed system is a combination of ideas presented above, using a distributed phased-array antenna system with electronically programmable hardware delays. A schematic of the system is shown in fig. 6. The array is initially configured for a low-power detection mode, in which we use the principles of the confocal imaging technique to find the location of the tumor. Once the position of the tumor is resolved satisfactorily, the array is then excited at a higher energy with the appropriate time-delays to create a high-energy "real" focal point at the tumor site to thermal destroy the tumor. The system can alternate between these two modes of operation to adaptively reshape the beam or focal point if necessary due to thermally-induced changes in the electromagnetic scattering properties. In addition, we anticipate using thermal sensors at the skin surface to assist in the mapping and localization of the tumor site, as well as monitoring the thermal destruction of the tumor.

Patch antennas on conformal substrates will be used for the array elements. Ultimately we anticipate a system such as shown in figure 7, in which the array elements are oriented on a spiral, which can be rotated around the subject for improved detection and mapping. The array electronics will use commercially available RF and MW components. In electromagnetic simulations using Finite-Difference Time-Domain (FDTD) techniques, Taflove has showed that a carrier frequency of 6 GHz resulted in optimum response and resolution using published data for the dielectric properties of breast tissue, so our initial array prototypes will be constructed for operation at this frequency.

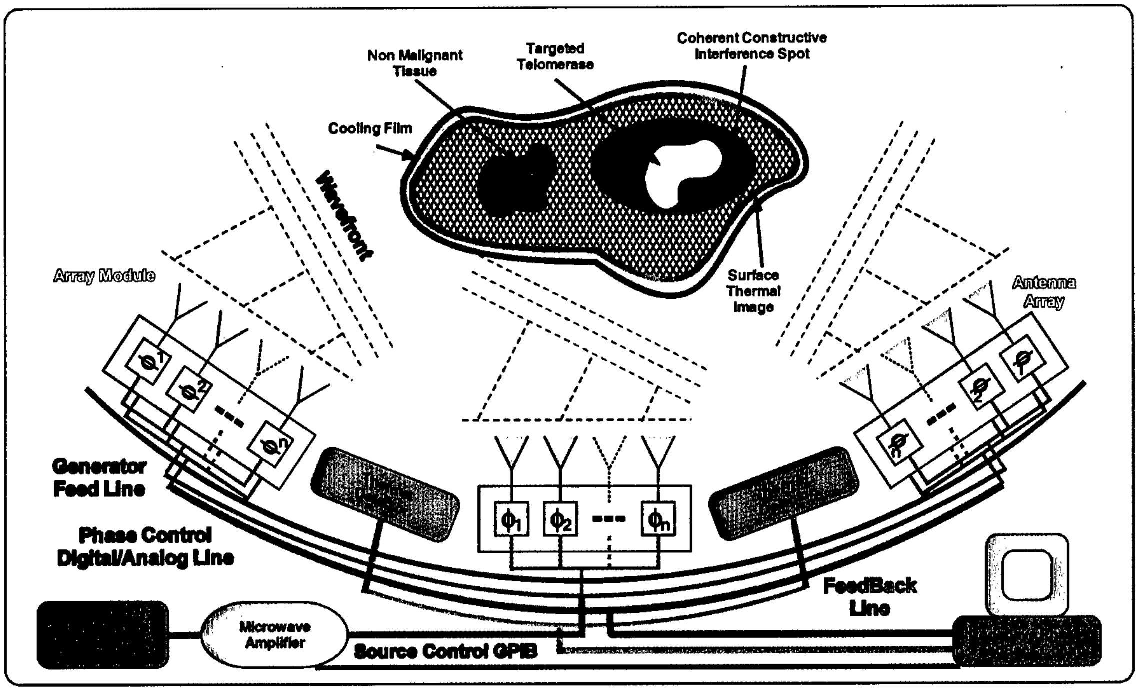


Figure 6 - Block diagram of the proposed detection/therapy system. Phased arrays are used to selectively illuminate a region and record the backscattered signal. If there is a cluster of relative high reflective material such as water in fats, the reflected signal gives detailed information on the location of the cluster. Once localized, the total energy is increased and focused at the tumor site to thermally destroy it.

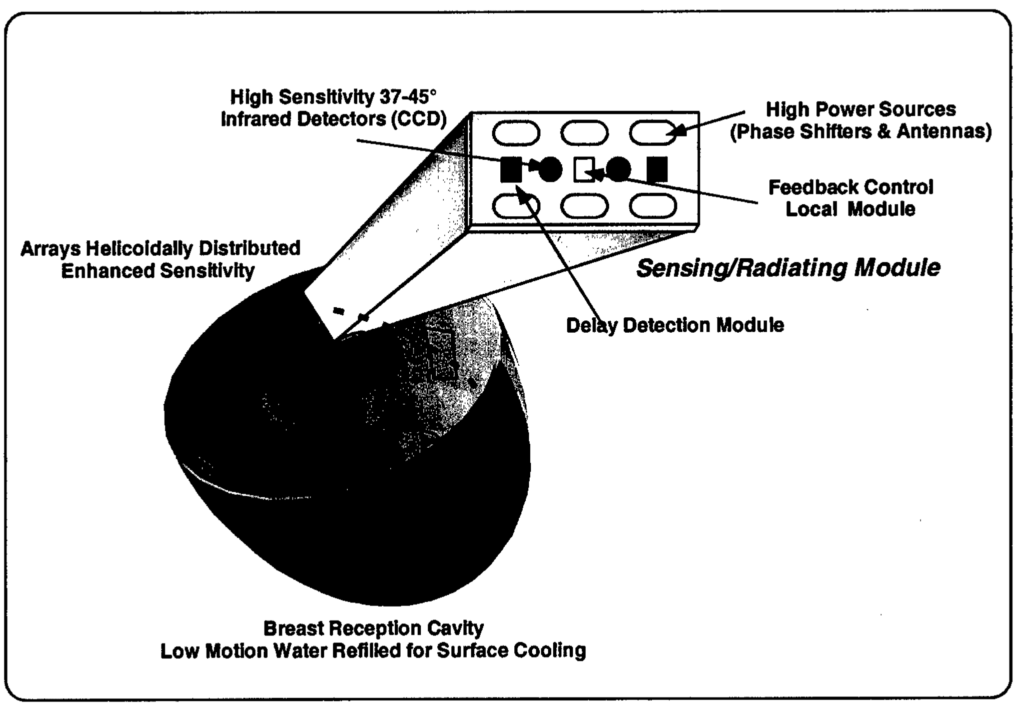


Figure 7 – Possible breast configuration of the proposed system: the phased arrays are distributed in a spiral on a rotating support to enhance the detection resolution, inside a cavity filled with water that slowly recycles to cool the skin surface.

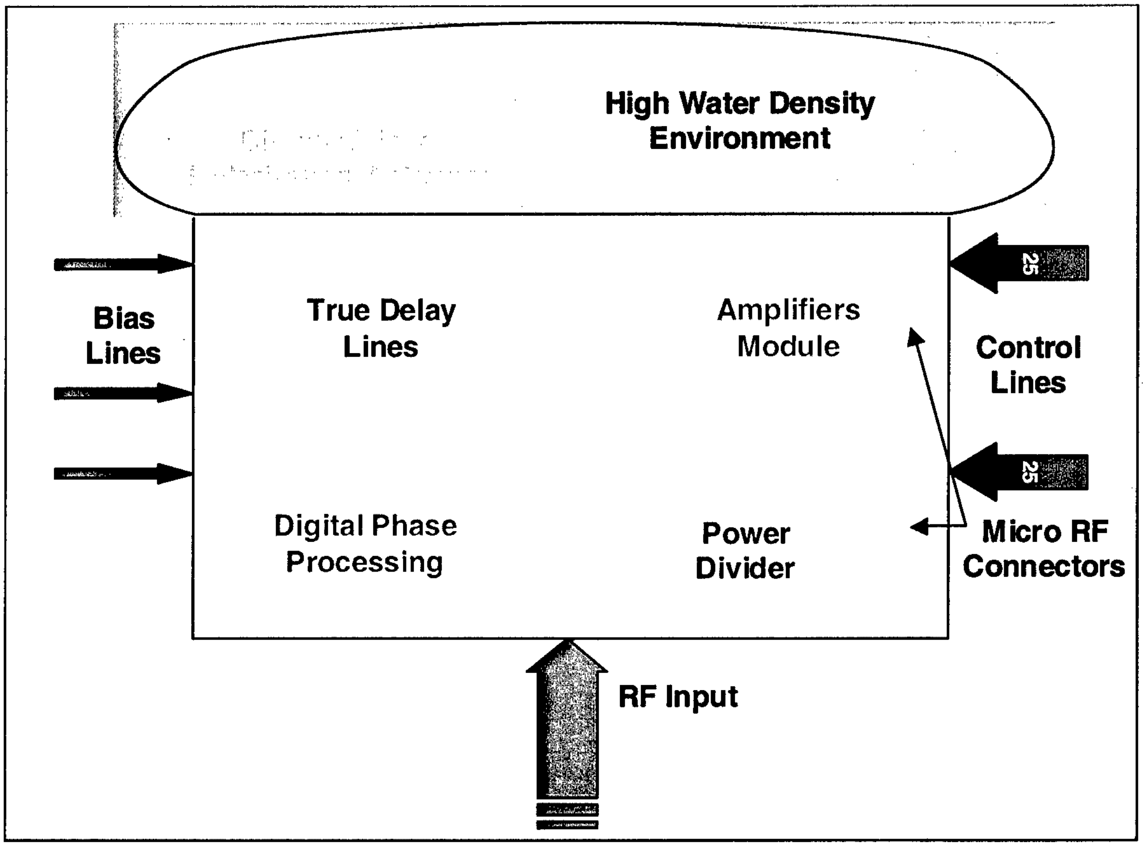


Figure 7 – Antenna array module made of 25 unit cells 1 cm x 1 cm size.

The proposed detection/therapy method is non-invasive, low risk and comfortable. Because of the high contrast in dielectric properties between tumor and healthy tissues in breast, neck and brain, this technique should already increase the effectiveness and comfort of the current detection/therapies. The first phase of this program will seek to build a complete hardware system and test on phantom subjects. Ultimately, we believe that such systems can be greatly enhanced through the development of markers that can be activated or strongly enhanced by means of microwave absorption. The small focus provided by multiple arrays will combine with the effect of the marker drug to provide a very selective thermal and or chemical destruction of malignant cell with very low risk for out of spot and marker inactive cells.

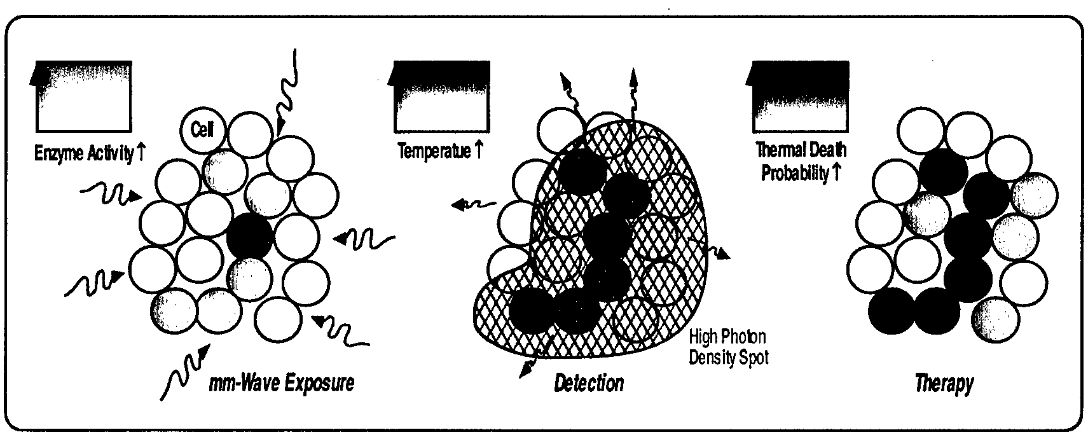


Figure 8 - Ultimate goal of the work is the detailed mapping of the marker activity followed by the focused microwave exposure that will cause the thermal death of the targeted cells

Our hardware system will not change, but its effectiveness will be enhanced while providing localized activation of marker drugs. Together with the enhanced therapy, the marker can also be used to improve the detection if highly reflective material, such as some polymers can be attached to it. The goal is to track down possible small metastatic clusters and detect tumors in early stages even in highly water contents region of the body.

The advantages of such a system can be thus summarized as:

- Accurate, low-risk non-invasive detection of small malignancies and mapping of large ones.
- Enhanced hyperthermia therapy with no skin-burns and deep selectivity due to focused coherent addition of low-intensity/low energy photon beams
- Safe and low-risk redundancy using two simultaneous non-invasive feedback mechanisms (3-D thermography and confocal imaging) to locate tumor sites.
- General detection/therapy for markable elements (i.e. Telomerase mapping)
- Communication market will drastically reduce the price of components & technologies

Early detection improves the outlook for success in patient treatment, and that we are extremely limited in our capabilities to identify the earliest stages of cancer as they emerge. Microwave phased array scanning can offer the technology platform on which the molecular changes can be non-intrusively monitored, allowing the identification of the earliest set of changes in each support the identification of the molecular signatures of cells and related resulting features of emerging cancers before surgical intervention is required.

Program Relevance

Recent studies showed that a particular enzyme called Human Telomerase could be used as malignancy marker in 90% of the cancerous forms. Its activity increases in those cells whose cycle does not shorten the tail of the DNA molecule called Telomere. The clock of cellular aging resides in this region. The telomere hypothesis proposes that as mortal cells divide, this DNA tail is progressively lost with each cell division. At the end of it the cell dies. To support this hypothesis is the fact that immortal cells like reproductive and malignant cells do not shorten their DNA tails. The enzyme rebuilds the same DNA sequence (TTAGGG) hundreds of times, effectively "capping" the ends in a manner similar to the way the plastic on the ends of our shoelaces "caps" and protects the shoelaces from unraveling. Its activity can be detected in reproductive and malignant cells.

Geron Inc. has cloned the two essential components of the Telomerase enzyme: the RNA template of Telomerase ("hTR") and the catalytic reverse transcriptase protein component ("hTERT"). Recent efforts from different institutions (UCSF) are aimed to find the crystalline form of this enzyme. The crystalline form will help in the selective attachment of chemoagents. The problem however is that the Telomerase is also present in embryos

and lynphocytes which regulates our immune system. Not localized activation of a drug directed to Telomerase can compromise the immune system[12].

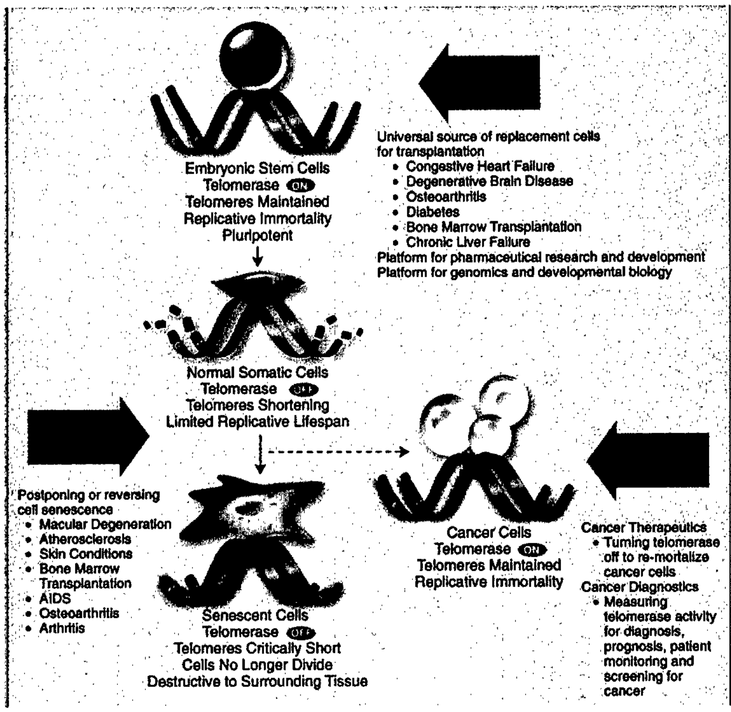


Figure 9 - Possible applications for telomerase (Geron Corporation).

The possibility to attach drugs that are activated (or enhanced) only with temperature increase may synergistically enhance our proposed system. There are extremely interesting organic and inorganic materials (such as polymers and zeolites), which are biocompatible and have scattering and absorbing properties that can enhance detection and thermal absorption at microwave. If the material has reflection/absorption properties (i.e. a complex dielectric permittivity) very different from the water, it will increase the scattering and thus the detection of cluster of such material in the human body even in tissues with high water content. Concerning the temperature enhancement, the cell thermal death is more selective as the conversion photon-thermal vibration is more efficient.

Telomerase can thus be used as an effective molecular signature for the following reason:

- At least 90% of malignant cell presents a high (~100) concentration of enzymes
- Not present in normal somatic cell but in embryonic ones
- It can be cloned

Another possible application target, if appropriate microwave activated drugs are developed, could be the hepatocyte growth factor (HGF). The Cancer Research Center in Candiolo (Italy) recently revealed that the interaction of the (HGF) with its receptor (Met Tyrosine Kinase) results in invasive growth, essential to embryonic development and implicated in tumor metastasis[13].

Part 2: Study of new microwave absorbing materials

Once we outlined the possible design for the new detection and therapy system, we focused our attention to identifying and measuring biocompatible materials that would enhance the absorption and/or the scattering of microwave photons in water based inhomogeneous medium. The first month was dedicated to deepening our understanding of dipolar polarization and conduction mechanisms, which determine the efficiency of microwave heating. A measurement system was then established and a series of measurements was taken on water-soluble conductive polymers.

A common misunderstanding that molecular motion, and thus heating, is caused by microwave absorption into rotational energy levels. However, it is gaseous water that has quantized rotational energy levels in the microwave region, and is thus responsible for heating.

In the liquid state, for all practical purposes, the quantization of rotational levels is non-existent. The easiest way to visualize the true mechanism is to picture microwaves for what they are - high frequency oscillating electric and magnetic fields. In this field, anything electrically or magnetically polarized at the oscillation frequency will be affected. Two phenomena occur normally in the heating process: dipolar polarization, and conduction mechanisms. A third mechanism – interfacial polarization – also occurs. This mechanism is of relevance in the case of small particles, such as those under investigation in this study.

Since heat is the form of energy transfer associated with two bodies at different temperatures, the first effect of microwave absorption in a particle cluster is the increase of its internal energy. This happens because as a particle follows the field, it instead finds the incoherent inertia of the particles in the cluster, due to their random initial polarization states. Then, if cluster entropy does not change significantly, its temperature will rise causing the system to transfer energy (as heat) to the surrounding environment at a lower temperature (k is the Boltzman's constant):

$$W_{In} \rightarrow U \nearrow \rightarrow T = \frac{\partial U}{k \partial \sigma} \nearrow \rightarrow Q_{Out}$$

The math of microwave properties

To understand quantitatively how materials react to microwave radiation, it is important to consider the concept of complex dielectric constant, ε^*, which describes the dielectric properties of homogeneous materials and is expressed as the sum of real and complex dielectric constants: $\varepsilon^* = \varepsilon' + i\varepsilon''$

The real part of ε^*, ε', represents the ability of a material to be polarized by an external electric field. At very high and very low frequencies, and with static fields, ε' will equal the total dielectric constant of the material. Where electromagnetic energy is converted to heat by the material, ε'' is non-zero, and quantifies the efficiency with which the electromagnetic energy is converted to heat.

A further quantity, the loss angle δ, is also commonly used in the literature, and is more usually given in the form of its tangent. It is related to the complex dielectric constant by $\mathrm{Tan}\delta = \frac{\varepsilon''}{\varepsilon'}$. The angle δ is the phase difference between the electric field and the polarization of the material.

Magnetic polarization may also contribute to the heating effect observed in materials where magnetic properties exist, and similar expressions for the complex permeability of such materials may be formulated. Although such cases are relatively uncommon, a familiar example of its importance is in the microwave heating of Fe_3O_4. Here, we will be focusing our attention on dielectric materials.

Dipolar Polarization[14]

Dipolar polarization is the phenomenon responsible for the majority of microwave heating effects observed in solvent systems. The different electronegativities of individual atoms result in the existence of a permanent electric dipole on the molecule. For a molecule in a polar liquid such as water (methanol, ethanol, THF, etc), there are intermolecular forces, which give any motion of the molecule some inertia.

The dipole is sensitive to external electric fields, and will attempt to align with them by rotation, the energy for this rotation being provided by the field. This realignment is rapid for a free molecule, but in liquids instantaneous alignment is prohibited by the presence of other molecules (intermolecular inertia). A limit is therefore placed on the ability of the dipole to respond to a field, which affects the behavior of the molecule with different frequencies of electric field.

Under very low frequency irradiation, the dipole may react by aligning itself in phase with the electric field uniformly and no significant random motion results. The molecule gains some energy, and some is also lost in collisions but the overall heating effect is small.

Under the influence of a very high frequency electric field, on the other hand, the dipoles will attempt to follow the field, but they do not have sufficient time to respond to the field, and so do not rotate. As no motion is induced in the molecules, no energy transfer takes place, and therefore, no heating.

Between these two extremes, at frequencies, which are approximately those of the response times of the dipoles, is the microwave region. The microwave frequency is low enough that the dipoles have time to respond to the alternating field, and therefore to rotate, but high enough that the rotation does not precisely follow the field. As the dipole reorients to align itself with the field, the field has itself already changed, creating aphase difference between the orientation of the field and that of the dipole. This phase difference is randomly distributed among the particles causes energy to be lost from the dipole in disordered collisions, and to give rise to dielectric heating.

For any material, both the real and complex dielectric constants will vary with frequency. The variation of ε' and ε'' with frequency for de-ionized (DI) water is shown in Figure 1.[15]

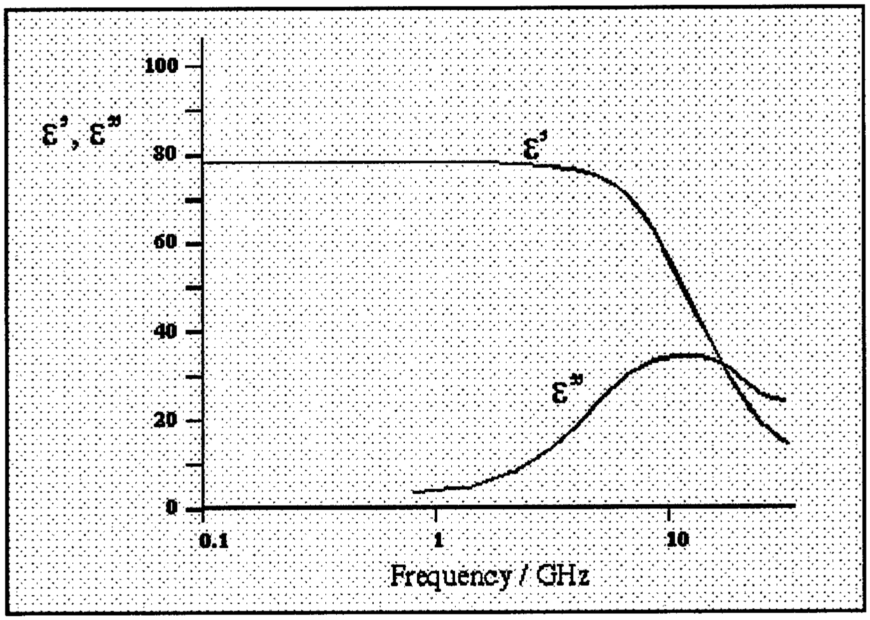


Figure 1: Complex dielectric constant for DI water in the microwave frequency range.

The difference is clear with quantum spectroscopic absorption: in the gas state the absorption linewidths are typically of the order of nanometers, while in the liquid state?, the range of frequencies over which the dielectric loss is non-zero is relatively large.

As we reach the maximum in the dielectric loss ε'', the dielectric constant ε' goes through a point of inflexion as it decreases with increasing frequency.

Our current understanding of dielectrics is strongly based the theoretical work of Debye[16,17] who expressed mathematically the frequency and temperature dependence of ε' and ε'':

$$\varepsilon^* = \varepsilon_\infty + \frac{\varepsilon_s - \varepsilon_\infty}{1 + i\omega\tau} \rightarrow \begin{cases} \varepsilon' = \varepsilon_\infty + \dfrac{\varepsilon_s - \varepsilon_\infty}{1 + \omega^2\tau^2} \\ \varepsilon'' = \dfrac{\varepsilon_\infty - \varepsilon_s}{1 + \omega^2\tau^2}\omega\tau \end{cases}, \text{ with } \tau = \frac{4\pi\eta r^3}{kT}.$$

In the previous expressions, ε_∞ and ε_s are the dielectric constants at very high and very low frequencies (static). Infrared and higher frequency resonances are not taken into account. Debye derived the relaxation time, τ, from Stoke's theorem using the molecular radius r, the viscosity η, the Boltzman's constant k and the absolute temperature T.

The importance of Debye's work is clear when plotting his equations normalized to the product frequency-relaxation time (as in Figure 2) and comparing them with the experimental values for de-ionized water. Most of the dielectric solvents show similar behavior.

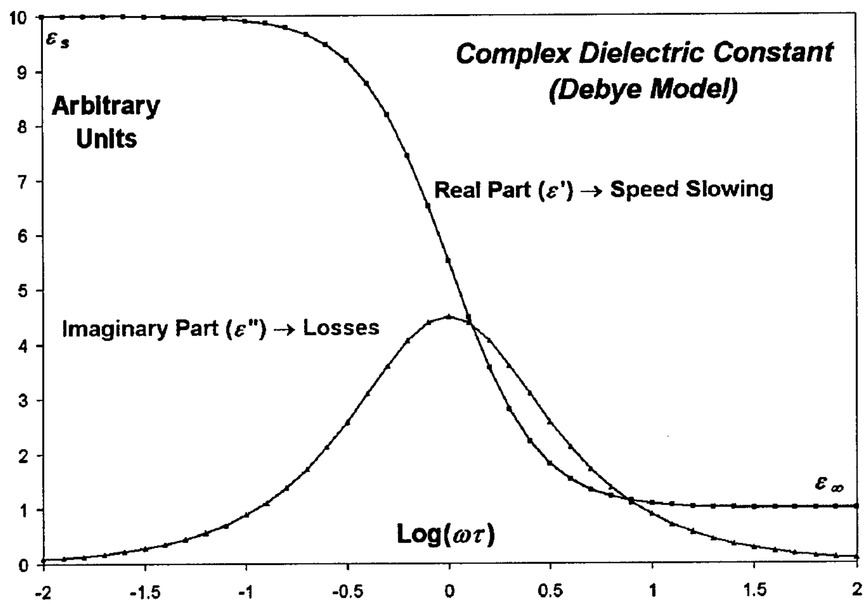


Figure 2: Debye's expressions for ε' and ε'' calculated as a function of $\omega\tau$ ($\varepsilon_s = 10$ and $\varepsilon_\infty = 1$).

Usually in medical and consumer applications the frequency of the electric field is chosen far from the maximum absorbency of water at 22 GHz, to have efficient heating, while avoiding absorption of energy not on the surface of the body or food.

Thus, we are interested in materials that present a very high absorption at a lower frequency than water, so that the heating process can be enhanced in the regions where the material is located within a water-based body. Thus, a larger relaxation constant is needed, while trying to keep the absorption as high as possible. Increasing the average dipole radius and the viscosity would be beneficial in that sense.

Water Isotope

As suggested by some data reported by NASA[18], an isotope of water has two interesting properties: it's very stable and in gas state as a resonant frequency in the range 5-6 GHz while normal water has it at ~22 GHz. If the resonant properties of this material are present also in the liquid phase, it would become an excellent candidate, since the absorption would be resonant (high peak), biocompatible (stable) and visible in MRI (isotope). Unfortunately phone and email conversations with Prof. Vladimir Gaiduk[19], lead to the conclusion that resonant states are very improbable in liquid state since the hydrogen bonds redistribute and spread the energy levels of the rotational and vibrational modes[20].

Conduction

Where the irradiated sample is an electrical conductor, the charge carriers (electrons, ions, etc) are moved through the material under the influence of the electric field, E, resulting in a polarization, P. These induced currents will cause heating in the sample due to any electrical resistance. This happens in the majority of solids, but it is also present in ionic solutions.

For a very good conductor, complete polarization may be achieved in approximately 10^{-18} seconds, indicating that under the influence of few GHz radiations, the conducting electrons move precisely in phase with the field. Thus, if the sample is too conducting (small resistance to charge movements), such as a metal, most of the microwave energy is reflected. This property can be used for imaging systems, which base their accuracy on the power reflected back from the target.

The complex dielectric constant may be expressed to take account of these losses by including a separate conduction term:

$$\varepsilon'' = \frac{\varepsilon_\infty - \varepsilon_s}{1+\omega^2\tau^2}\omega\tau - \frac{\sigma}{\omega\varepsilon_s}$$

For example, if one takes pure water and heats it in a microwave oven, where the polarization mechanism dominates, we find that the heating rate is significantly less than if one takes the same volume of water and adds salt. In the latter case, both mechanisms occur, increasing the heating effect.

Interfacial Polarization

This mechanism is important for systems comprised of conducting inclusions in a second, non-conducting material. An example would be a dispersion of metal particles in sulphur. Sulphur is microwave transparent, while metals reflect microwaves; however, the combination forms an extremely good microwave absorbing material (so good, in fact, that interfacial polarization effects are the basis of 'Stealth' radar absorbent materials)[21].

Where a dielectric material is not homogeneous, but consists of inclusions of one dielectric in another, it is still possible theoretically to treat the material. If the dielectric properties and geometry of the inclusions are known, it is possible to arrive at expressions for the dielectric behavior of the bulk sample. However, determining the dielectric properties of the components from that of the system is generally insolvable except in the simplest of cases.

For a (non-superconducting) metal, there will always be a very thin surface layer in which some of the incident microwaves are attenuated, and in which induced currents will give rise to heating. For a bulk metal, this heating effect is so small as to be irrelevant, but in powders this surface layer makes up a large proportion of the material. However, the polarization induced in the metal is also subject to the properties of the surrounding medium, decreasing its effectiveness. Under these circumstances, the polarization of the metallic particles does not take place instantaneously, but lags behind the induced field, because of the polar molecule in the dipolar polarization mechanism. Hence, the frequency dependence of the sample's heating properties is similar to that of the dipolar polarization mechanism, despite being in actuality a conduction mechanism. Thus, interfacial polarization is most easily viewed as a combination of the conduction and dipolar polarization effects.

To derive a model for this phenomenon, the most basic geometrical situation was considered by Maxwell[22]. This consisted of a plate capacitor of n dielectric sheets of dielectric properties and conductivities $\varepsilon_1\ \sigma_1$, $\varepsilon_2\ \sigma_2$, ... $\varepsilon_N\ \sigma_N$. Maxwell showed his model to be capable of explaining the observed data for dielectric relaxation in such systems.

Wagner[23] and Sillars[24] developed further Maxwell analysis for spherical enclosures. Their models led to expressions similar to the Debye's equations. The

original values of τ, ε_∞ and ε_s are modified to an effective value dependent on particle relative size and the volume fraction.

In reality little can be deduced about the dielectric properties of a heterogeneous material unless the shapes of the inclusions are well known. Agreement of the theoretical models with real systems has been demonstrated by the inclusion of 3% copper phthalocyanine in paraffin wax[25]. At higher concentrations, interparticle electrostatic interactions must be taken into account. Attempts to do this have shown reasonable agreement with up to 30% water droplets in woolwax .13 and with 27.5% nitrobenzene in polystyrene[26] (Figure 3).

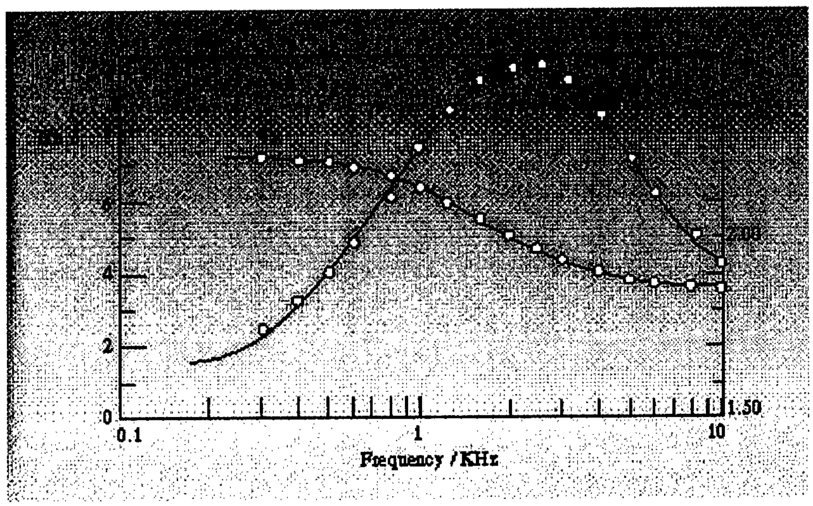


Figure 3: Dielectric properties of 27.5% volume nitrobenzene in polystyrene (Upper curve of each pair are experimental measurements, lower curve is the theoretical values)

Thus, when studying small conductive particles immersed in a dielectric, this phenomenon may lead to interesting properties. For this reason, we are focusing our attention on conductive polymers immersed in water and other biocompatible solvents. Together with the heating, these surface currents may lead a small polymeric enclosure (such as liposome) to break and release its content under low power microwave radiation. If the polymer does not absorb the microwave energy efficiently, it may still be so conductive that it scatters the energy, thus enhancing microwave detection systems. Conductive polymers seem to be a promising choice in this direction.

Conductive Polymers

Alongside ceramic processing, polymer chemistry forms probably the largest single discipline in microwave chemistry. The dielectric properties of polar starting materials and very often products are an excellent indicator of reaction progress. The ability to control syntheses with high accuracy and with direct heating of the reactants has the advantage of large potential savings in energy. Economic analyses suggest that the costs of curing polymers may be reduced of a factor of 10 by switching to the use of microwaves[27].

Investigations have indicated that the rate of curing depends less upon the total power than on the method through which microwave pulses are applied to a sample. This is most probably related to the relaxation mechanism involved in the polymeric reaction.

For example, with the epoxy resin DDS (4,4' diaminophenolsulphone), short high power pulses with a low time-averaged power ($2x10^{-3}$ sec, 700 Watts) were found to give comparable results to those of longer pulses, with high time-averaged power ($2x10^{-2}$ sec, 1500 Watts)[28,29]. Moreover, the pulse causes selectivity in bond formation: self-polymerization is preferred under short pulse irradiation. For each reaction (such as a cross-link) it seems to exist an optimum pulse frequency based on the polar linking agent[30,31,32].

These studies together with others[33,34], seem to suggest that energy transfer is more efficient with the use of pulsed microwaves than by continuous power at least when polymers are in a heterogeneous medium. Inherently[35] conducting polymers such as polyaniline p-toluene sulphonate or polypyrrole p-toluene sulphonate are excellent microwave absorbers and are commonly used in welding of plastics.

Recent studies[36] attempt to explain the observed phenomena with relaxation processes occurring at different sites of the molecules. The imaginary part of the complex dielectric constant can be still expressed as the sum of polarization and conduction. We are in the progress of deepening our understanding of these models in order to interpret correctly the results presented below.

Measurement Setup and Calibration

We are interested in measuring the complex dielectric constant of liquid materials in the frequency range 20 MHz – 2 GHz using two methods: the reflection and the transmission techniques. In the reflection technique, the microwave power is sent to one side of the sample through a probe and the scattered power is recollected from the same side. In the transmission technique, the power is sent from both sides using a transmission line with the sample inside. This method provides multiple means by which to calculate the dielectric properties, all of which can be combined to increase accuracy.

Due to the high price (15k$) of commercial transmission-based systems, we are in the process of constructing our own transmission lines to confirm the results that we are collecting with the HP 85070 dielectric probe, which is based on the reflection method.

Both techniques make use of a network analyzer that sends and recollects microwave power and calculates the ratios of reflected and transmitted to incident powers.

The HP 85070 kit allows measurements of the complex permittivity for a wide range of semi-solid, pliable-solid, and liquid materials in the range 0.02-20 GHz. It performs all of the necessary network analyzer control, calculation, and data presentation functions. The software controls the network analyzer to measure the complex reflection coefficient of the material under test (MUT). Then it converts the reflection coefficient into the complex permittivity of the MUT. Finally it displays the measurement results in a variety of graphical and tabular formats.

The dielectric probe provides a convenient and repeatable method for measuring various dielectric materials. The convenience is a result of needing only to press the probe against (or immerse it in) the MUT to make a measurement. The probe is used with a vector network analyzer, in our case the HP8722D to take advantage of the analyzer's measurement flexibility, speed, and accuracy. Use of the vector network analyzer allows the software to calibrate against a variety of measurement errors and thus enhance accuracy.

An additional adjustable stand is used to adapt the probe to the samples dimensions (Figure 4).

This system needs to be calibrated as the external surroundings, especially metal parts, influence the measurements. Assuming that the environment does not change significantly, we can correct the measurements based on environmental influences. This calibration process needs to be performed also when the sample size changes, as container walls and the metal stand would affect the results.

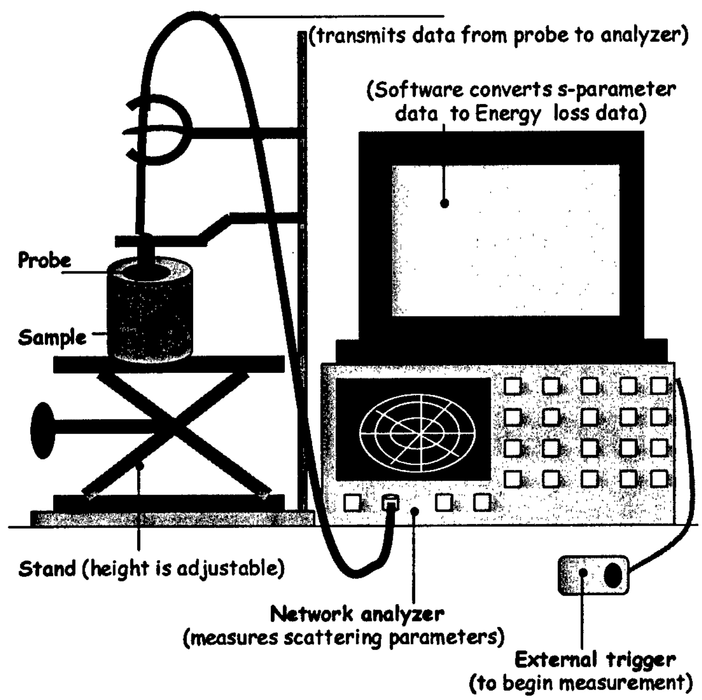
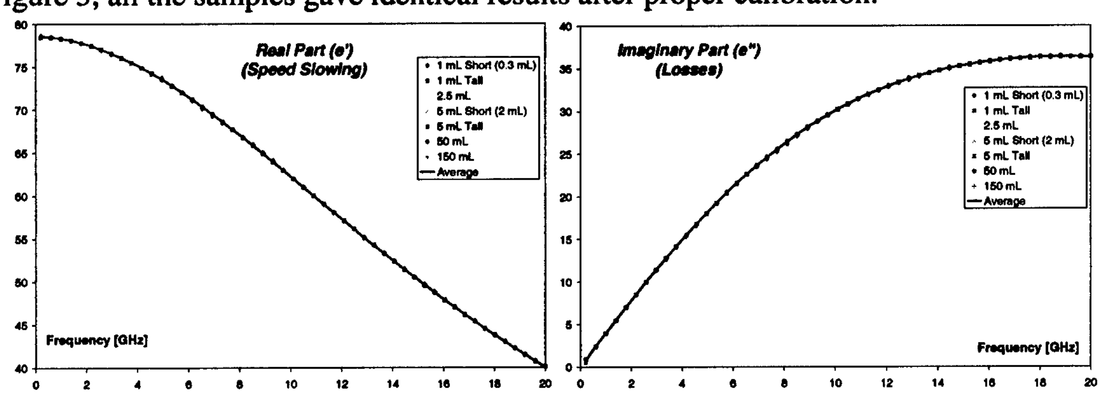


Figure 4: Reflection-based measurement setup.

First of all, due to the price of the materials under investigation♣ only a limited amount was available (1-2 mL). Thus initially it was necessary to prove that container size could be reduced to 0.3 mL with the proper calibration without affecting the quality of the results. We performed these measurements with DI (define, please) water. As shown in Figure 5, all the samples gave identical results after proper calibration.



♣ One of the material is an expensive isotope of water and the other is a mixture of water-soluble conjugated polymers, which is still in its experimental stage.

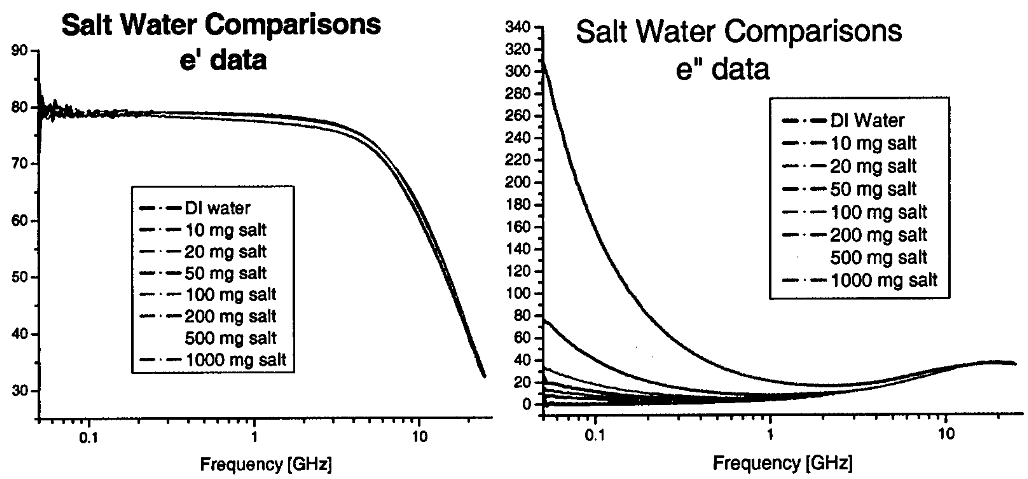
Figure 5: Imaginary and real part of the complex permittivity of DI water for several sample sizes.

Samples Measurements and Results Interpretation

Once the dimension of the sample was no longer a concern we performed our measurements. Here we list only the most significant ones that gave a response to the previous questions and the interpretation of their properties is presented.

Ionic Solutions

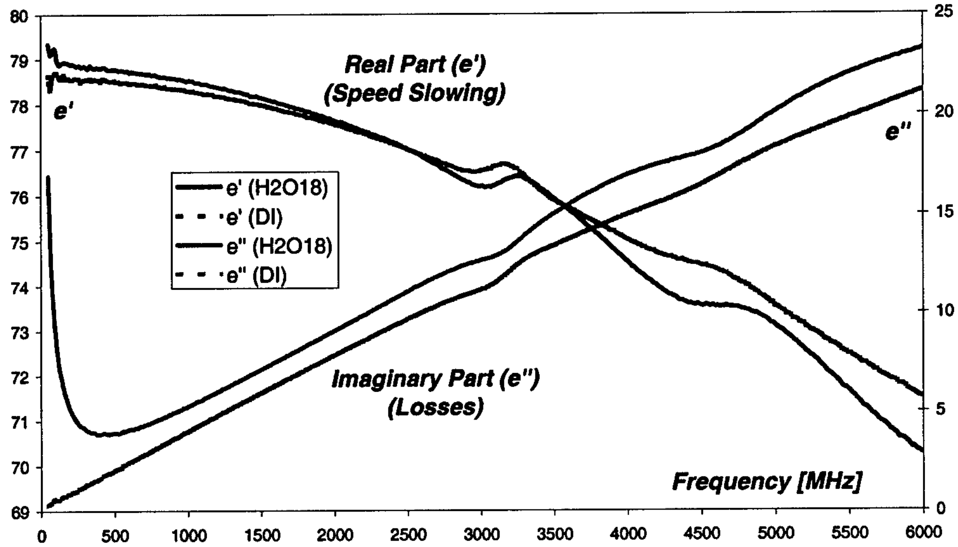
We measured ionic solutions with different salt concentration in DI water. These measurements gave us an idea of the influence of ionic substances in the samples in orther to be able to give a first qualitative interpretation of the different materials and identify in their properties the contribution of conduction effects



The results clearly highlight the strong contribution of the ionic species to the absorption mechanism (e''), but e' does not change significantly.

H_2O^{18}

We measured the previously mentioned isotope of water: the solution was 87.5% H_2O^{18} and 12.5% H_2O^{16}. It was measured at room temperature (25°C) in the range the 20 MHz to 2 GHz frequency range.



These results clearly suggest higher energy absorption than normal DI water in the whole range, with a drastic increase of loss at lower frequency where current microwave phased array thermal therapy is applied (100-200 MHz)[37].

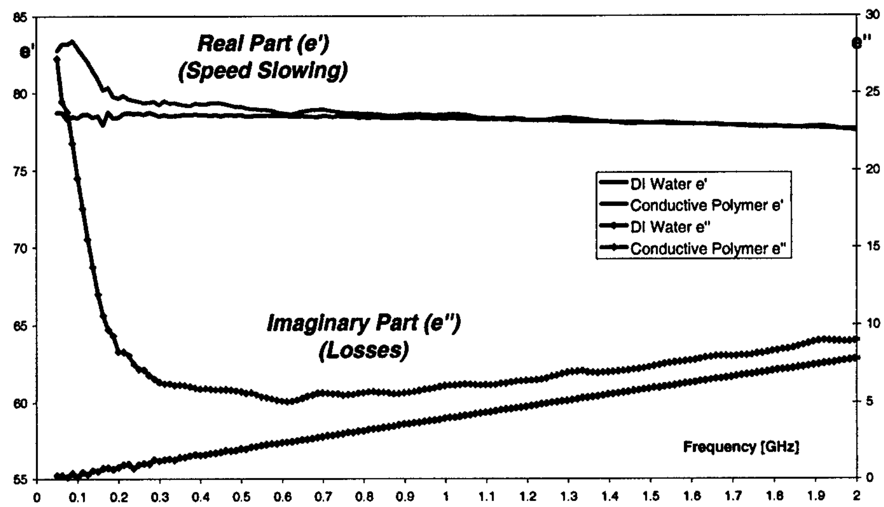
Repeated measurement proved that the glitch at the center of the plot is due to calibration difficulties at around 3 GHz.

As expected, we didn't find a resonant (strong absorption peak) rather a distributed absorption compared to normal DI water, as the hydrogen bonds redistribute the energy levels of the rotational and vibrational modes.

The strong absorption could anyway be explained if some salt was present in the solutions, as the company producing the isotope doesn't specify the resistivity of the samples. Isotopes provided by other companies could prove if the absorption is proper to the isotope or not.

Conductive Polymer

We measured a mixture of water-soluble conducting polymers[38]. Since the material is relatively new, to our knowledge, these measurements are the first to be performed at the 20 MHz to 2 GHz frequency range.



These results clearly suggest higher energy absorption than normal DI water in the whole range, with a drastic increase of loss at lower frequency where current microwave phased array thermal therapy is applied (100-200 MHz)[39].

As expected these results are difficult to fully interpret, due to the combination of dielectric polarization and conduction effects. They need to be confirmed and compared to the ionized water (with salt concentration of a typical human body).

Again it still needs to be understood if this is a results of ionic species or proper to the materials dynamics, since it could well be that the anodic and the cathodic portions of the polymer act as the salt previously presented. As expected, we didn't find a resonant (strong absorption peak) rather a distributed absorption compared to normal DI water, as the hydrogen bonds redistribute the energy levels of the rotational and vibrational modes.

Future work may include further measurements that will help improve the understanding of their relaxation process.

Key Research Accomplishments

- We investigated a novel hyperthermia system enhanced by confocal microwave detection and absorbing/scattering material encapsulated in liposomes.
- Deepen the understanding of microwave absorption phenomena and suggested possible class of materials suitable for enhancing hyperthermia treatment and tumor detection.
- First (at our knowledge) measurement of microwave dielectric properties of liquid H_2O^{18} water isotope.
- First (at our knowledge) measurement of microwave dielectric properties of a solution of water-soluble conjugated polymers.
- These results suggest higher energy absorption than normal DI water in the whole range 20 MHz-2 GHz, with a drastic increase of loss at lower frequency where current microwave phased array thermal therapy is applied (100-200 MHz)[40]. It still needs to be understood if this is a results of ionic species or proper to the materials under study.

Conclusions and Future Work

This research work was devoted to the development of a novel concept to enhance tumor detection and treatment using hyperthermia controlled by confocal detection. The enhancement of this system could be theoretically achieved with highly absorbing/scattering materials.

In this report we presented the two aspects of our research activity.

From one side we improved our knowledge of the current methods to detect and treat cancer with microwave systems. As a result we proposed a novel system for microwave power delivery controlled by a confocal detection mechanism.

The second part of our work consisted in understanding the mechanisms of dielectric absorption and scattering as well as to perform for the first time dielectric measurements of few materials suggested to enhance the hyperthermia treatment and the tumor detection. In the materials under study we found higher energy absorption than normal DI water in the whole range 20 MHz-2 GHz, with a drastic increase of loss at lower frequency where current microwave phased array thermal therapy is applied (100-200 MHz)[41]. It still needs to be understood if this is a results of ionic species or proper to the materials dynamics. As expected, we didn't find a resonant (strong absorption peak) rather a distributed absorption compared to normal DI water, as the hydrogen bonds redistribute the energy levels of the rotational and vibrational modes.

Future work could provide additional materials to test based on the presented absorbing phenomena. The encapsulation of the selected material in a vector such as a liposome could be the next step followed by the analysis of the leakage, the heating efficiency and scattering properties of such systems. The final goal should be the optimization of the microwave power delivery system based on the frequency and type (pulsed versus continuum energy) that make best use of the material properties.

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